wherein n is 0 or 1, and R is selected from the group consisting of C_{1-10} alkyl, C_{6-10} aryl and

and wherein when n is 0, R is not C_{6-10} aryl.--

REMARKS

Upon entry of the present Amendment, claims 1-21 will be pending. The Abstract has been amended to include chemical formulas of exemplary compounds of the present invention. Claims 1, 8 and 9 have been amended to correct typographic error and/or to remove multiple dependency in the claims. Therefore, the above-described amendments do not introduce any new matter into the present application.

Applicants appreciate the Examiner's withdraw of the following objections/rejections:

- The objection to the claims set forth in paragraph 3 of the previous Office Action in Paper No 4.
- The rejections under 35 U.S.C. § 112, second paragraph, set forth in paragraphs 4 and 5 of the previous Office Action in Paper No 4.
- The rejection under 35 U.S.C. § 102 (b) set forth in paragraph 6 of the previous Office Action in Paper No 4.
- The rejection under 35 U.S.C. § 103 set forth in paragraph 7 of the previous Office Action in Paper No 4.

Applicants noticed that References 13-17 submitted with the June 27, 2002 Information Disclosure Statement have not been initialed. Applicants respectfully request the Examiner to consider and make the references of record in the present application.

Specification

The abstract of the disclosure is objected to because it allegedly does not summarize the contribution that the instant invention makes to the art. The Examiner states that Applicants should include a description (chemical name or structure) of the compounds of the invention.

This objection is overcome by the amendment of the present Abstract.

Claim Objections

Claims 8 and 9 are objected to under 37 C.F.R. 1.75(c) as allegedly being in improper form because a multiple dependent claim since claims 8 and 9 each depend upon two claims (5 and 2, 5 and 3, respectively).

These rejections are overcome by the amendment of claims 8 and 9.

Rejection under 35 U.S.C. § 112

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that claim 1 recites the limitation "C_6-C_{10}" in line 4. The Examiner alleges that claim 1 and its dependents are therefore rendered indefinite. The Examiner suggests that Applicants add the word "aryl" after the indicated limitation.

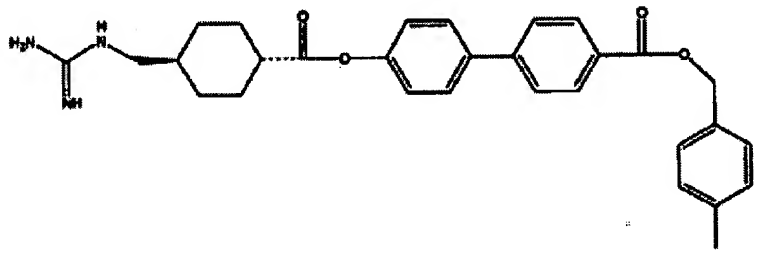
This rejection is overcome by the amendment of claim 1.

It is respectfully submitted that the rejection of claims 1-21 under 35 U.S.C. § 112 is overcome by the above remarks and/or amendments and must be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Kamoda *et al.* (US 6,284,791 09-2001) (Kamoda) and further in view of Satoh *et al.* (US 4,732,916 03-1988) (Satoh).

Kamoda is alleged to teach the following compound as a racemic mixture:



Kamoda is also alleged to teach the following:

- the activity of the compound against *Helicobacter pylori* and *Eschericia coli* (Column 37, lines 33-64, Table 1, 14th entry);
- methods of treatment and pharmaceutical compositions (with excipients, etc.) of the compounds disclosed for oral administration to humans (Column 12, line 57-column 13, line 31); and
- combination therapies using the combination of antibiotics such as amoxicillin and omeplazol, lansoplazol (*anti-H. pylori agents*) which comprises inhibition activity to a proton pump and are used in clinics as anti-ulceration agents and compounds containing the guanidine group to treat conditions such as gastritis (Column 1, line 33 - column 2, line 5).

The Examiner acknowledges that the difference between the instant invention and that that taught by Kamoda is that Kamoda does not suggest replacing the saturated cyclohexane ring with an aromatic benzene ring.

The Examiner alleges, however, Satoh teaches (Column 1, lines 17-44) that the replacement of the cyclohexane ring in the compounds of Kamoda with an aromatic benzene ring

results in an increase in anti-ulcer activity and a decrease in toxicity. The Examiner also alleges that Satoh's teaching can therefore be seen as a suggestion to modify the compounds disclosed by Kamoda to arrive at the instant compound of claim 3.

The Examiner concludes that the instantly claimed compounds and methods would have been obvious to one of ordinary skill in the art. The Examiner states that the motivation would have been to produce an anti-ulcer treatment that was more effective (increased potency) and less toxic. The Examiner also states that the expectation for success would have been high since Satoh teaches the instant modification of Kamoda's compounds.

This rejection is respectfully traversed. Kamoda and Satoh, whether alone or in combination, do not render the presently claimed invention obvious for the following reasons.

There is no motivation, whether explicitly or implicitly, to combine the teachings of Kamoda and Satoh to arrive at the presently claimed compounds, pharmaceutical compositions, methods, combinations and kits. As acknowledged by the Examiner, Kamoda does not teach or even suggest replacing the saturated cyclohexane ring with an aromatic benzene ring. The entire motivation to combine the teachings of Kamoda and Satoh is based on the assumption that Satoh teaches the replacement of the cyclohexane ring in its own compounds with an aromatic benzene ring and such replacement results in an increase in anti-ulcer activity and a decrease in toxicity. The Examiner's assumption, however, is incorrect in at least two aspects. First, compared to NE-2001, the compound claimed in claim 2 of the present application, Satoh Compound I, the compound relied on by the Examiner, has no or negligible anti-*H. pylori* activities (*See* Supplemental WANG Declaration at paragraphs 13-15 and Table 1). Second, the ulcers treated by the Satoh Compound I are ulcers induced by stress, ethanol and indomethacin (*See* Satoh at column 3, line 37 through column 5, line 20 and Table 1). Satoh teaches or suggests nothing about any disease or disorder caused by *H. pylori* infection, let alone teaches or suggests combining its compounds with those of Kamoda to arrive at the presently claimed compounds, pharmaceutical compositions, methods, combinations and kits.

Another fallacy of the Examiner's reasoning for motivation to combine Kamoda and Satoh to arrive at the presently claimed invention is that it assumes that there is a close structural similarity between compounds taught in Kamoda or Satoh and the presently claimed compound,

i.e., compound of claim 2. However, such close structural similarity usually only exists between position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, *e.g.*, by -CH_2- groups). MPEP 2144.09. Isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other. *Ex parte Mowry*, 91 USPQ 219 (Bd. App. 1950) (claimed cyclohexylstyrene not *prima facie* obvious over prior art isohexylstyrene). Similarly, homologs which are far removed from adjacent homologs may not be expected to have similar properties. *In re Mills*, 281 F.2d 218, 126 USPQ 513 (CCPA 1960) (prior art disclosure of C_8 to C_{12} alkyl sulfates was not sufficient to render *prima facie* obvious claimed C_1 alkyl sulfate).

In the present case, comparing the compounds taught in Kamoda and Satoh and the compound of claim 2, they are neither isomers nor homologs. These compounds have different empirical formulas! It is not proper to compare only the portion of the presently claimed compounds that is different from the prior art compounds to the corresponding portion of the prior art compounds. Rather, the presently claimed compounds must be compared with the prior art compounds as a whole. MPEP 2141.02 *citing Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); and *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious); and *citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole."). Compared at the whole compound level, the compounds taught in Kamoda and Satoh and the compound of the present claim 2 have different empirical formulas and are not structurally related at all. In addition, even comparing the saturated cyclohexane ring in the compounds taught in Kamoda with the aromatic benzene ring in the compound of present claim 2, the saturated cyclohexane ring and the aromatic benzene ring have different empirical formulas, have different chemical structures and have different stereochemical structures (*See* WANG Declaration at paragraphs 2-4 submitted with the June 27, 2002 Amendment). Similarly, NE-2001 is a four-benzene ring

compound linked by two ester bonds; the compound described in Satoh is a two-benzene ring compound linked by a peptide-bond (*See* Supplemental WANG Declaration at paragraph 14). The linkage between these two compounds is entirely different. Therefore, their molecular structures and associated physicochemical prosperities are distinctly different.

Further, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. MPEP 2144.09 *citing In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (Affidavit evidence which showed that claimed triethylated compounds possessed anti-inflammatory activity whereas prior art trimethylated compounds did not was sufficient to overcome obviousness rejection based on the homologous relationship between the prior art and claimed compounds.); and *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967) (a 7-fold improvement of activity over the prior art held sufficient to rebut prima facie obviousness based on close structural similarity). Here, the present inventors have conducted experiments and demonstrated advantages of the compound of present claim 2 (NE-2001) over the compound disclosed in Satoh in that NE-2001 has strong anti-*H. pylori* activities whereas Satoh Compound I relied on by the Examiner has no or negligible anti-*H. pylori* activities (*See* Supplemental WANG Declaration at paragraphs 13-15 and Table 1).

It is respectfully submitted that the rejection of claims 1-21 under 35 U.S.C. § 103 is overcome by the above remarks and must be withdrawn.

CONCLUSION

Applicants submit that the rejections of claims 1-21 under 35 U.S.C. §§ 103 and 112 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 1-21 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to

charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952 referencing docket no. 524022000100.** However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: March 26, 2003 By: _____

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